Docket No.: 27611/37824A
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Anil Gulati

Application No.: 10/301,449 — Confirmation No.: 8744

Filed: November 21, 2002 — Art Unit: 1617

For: Method and Composition for Potentiating an Opiate Analgesic — Examiner: Shobha Kantamneni

DECLARATION OF ANIL GULATI UNDER 37 C.F.R. §1.132

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Dear Sir:

NOW COMES ANIL GULATI, Declarant herein, and states as follows:

1. I am the inventor of the invention disclosed and claimed in the above-identified patent application.

2. I am an Associate Dean for Research and Professor, Department of Pharmaceutical Sciences, Midwestern University, and am a Fulbright Scholar Grantee for 2008 to 2009. I also am an Adjunct Professor of Bioengineering, University of Illinois at Chicago. My peers consider me a world leader in the field of blood substitutes and endothelin research. As a researcher in pharmacology, I have established authored more than 250 publications in peer reviewed journals with international circulation and more than 270 abstract presentations. I have guided the research of 50 graduate students and research fellows.

3. I received a Ph.D. in Pharmacology from Erasmus University Rotterdam, The Netherlands (1996), a diplomat from the American Board of Clinical Pharmacology (1992), an M.D. (Pharmacology) from King George's Medical College, Lucknow, India

(1982), and an M.B., B.S. (Medicine) from King George's Medical College, Lucknow, India (1977).

4. I have conducted research in the fields of endothelins and blood substitutes since 1987. I am a named inventor in 18 patent applications, including two issued patents. I attach my full *curriculum vitae* as Exhibits A and B, which fully demonstrate my training and experience in the field of endothelins.

5. I have read and understand the Office Action dated April 15, 2008, which was issued in connection with U.S. Patent Application Serial No. 10/301,449. I also have read and understand the following patents cited by the examiner in U.S.S.N. 10/301,449:

Lebwohl U.S. Patent No. 6,573,285 ('285 patent)
Davar U.S. Patent No. 6,673,832 ('832 patent).

6. Claims 2-7, 9, 26, and 32, all of the claims in the application, have been rejected as being obvious over a combination of the patents listed in paragraph 5. The basis of the rejection is that (a) the '285 patent teaches treating pain with BMS 182,874 (an endothelin antagonist), and that an endothelin antagonist can be used in combination with another compound, like a narcotic, to treat pain, and (b) the '832 patent teaches treating a human to alleviate pain from conditions associated with increased ET-1 levels by administering an endothelin antagonist. Office Action, page 3.

7. From my review of the patents cited against the claims of the above-identified application, it is evident that *no* cited reference taught, suggested, or even considered the advance in the art provided by the present invention, i.e., the reduction or reversal of opiate tolerance in an individual undergoing opiate therapy by the administration of an ET_A antagonist, i.e., BMS 182,874. First, it is an important distinction that the claims in the above-identified application are directed to a method or reducing a reversing tolerance to an opiate analgesic, as opposed to the treatment of pain. From both my training and experience and that of others in the art, references relating to the treatment of pain cannot be correlated to the reduction or reversal of opiate tolerance.

8. It is known and reported that opiate analgesia and opiate tolerance are mediated through different mechanisms. It was found that the central serotonergic system is a key component of supra-spinal pain modulatory circuitry mediating opioid analgesia, and further that the mechanism of morphine tolerance and morphine reward are *independent* of the central serotonergic system (Zhao, Z. Q., Y. J. Gao, et al. (2007) "Central serotonergic neurons are differentially required for opiate analgesia but not for morphine tolerance or morphine reward." Proc Natl Acad Sci U S A **104**(36): 14519-24). The Zhao et al. publication provides genetic evidence indicting that central 5-HT neurons are necessary for opiate analgesia, but that morphine tolerance develops *independent* of central 5-HT neurons.

9. Additional evidence of the different mechanisms involved in opiate analgesia and opiate tolerance is found in the observation that okadaic acid (a selective inhibitor of serine/threonine protein phosphatases) antagonized, in a dose-dependent manner, the antinociceptive effect of morphine in morphine-naïve animals, but not in morphine-tolerant mice (Ocana, M., J. M. Entrena, et al. (2007) "The antinociceptive effect of morphine is reversed by okadaic acid in morphine-naive but not in morphine-tolerant mice." Pharmacol Biochem Behav **86**(1): 21-6). There also is evidence that in addition to mu-opioid receptors, an additional involvement of delta-opioid receptors in morphine tolerance occurs, and that delta-opioid receptor antagonists (Abdelhamid, E. E., M. Sultana, et al. (1991) "Selective blockage of delta opioid receptors prevents the development of morphine tolerance and dependence in mice." J Pharmacol Exp Ther **258**(1): 299-303) and delta-opioid receptor knock-out mice (Nitsche, J. F., A. G. Schuller, et al. (2002) "Genetic dissociation of opiate tolerance and physical dependence in delta-opioid receptor-1 and preproenkephalin knock-out mice." J Neurosci **22**(24): 10906-13) were shown to disrupt the development of tolerance.

10. Studies have demonstrated the importance of neurotransmitters and their interactions with opioid pathways in the development of tolerance to morphine. Blockade of glutamate actions by NMDA (N-methyl-D-aspartate)-receptor antagonists blocks morphine tolerance (Trujillo, KA and Akil, H, 1991, Inhibition of morphine tolerance and dependence by the NMDA receptor antagonist MK-801; Science **251**: 85-87). However, NMDA antagonists have no effect on the potency of morphine. Therefore, their effect cannot be attributed to potentiation of opioid actions (Gutstein and Akil 2006, "In Goodman and

Gilman's The Pharmacological Basis of Therapeutics, Eleventh Edition," Editor L.L. Brunton, Section III, Chapter 21, page 563).

11. Therefore, because a particular nonopiate compound may treat pain, this effect cannot be related to the different phenomena of opiate tolerance.

12. There are studies indicating the involvement of endothelin ET-1 in peripheral nociceptive transmission by activation of ET_A receptors (Baamonde, A., A. Lastra, et al. (2004) "Involvement of endogenous endothelins in thermal and mechanical inflammatory hyperalgesia in mice." Naunyn Schmiedebergs Arch Pharmacol 369(2): 245-51; Jarvis, M. F., J. L. Wessale, et al. (2000). "ABT-627, an endothelin ET(A) receptor-selective antagonist, attenuates tactile allodynia in a diabetic rat model of neuropathic pain." Eur J Pharmacol 388(1): 29-35; Peters, C. M., T. H. Lindsay, et al. (2004). "Endothelin and the tumorigenic component of bone cancer pain." Neuroscience 126(4): 1043-52). However, the mechanism of nociceptive action of ET-1 appears to be mediated through transient receptor potential vanilloid subfamily 1 (TRPV1), a capsaicin receptor. ET-1 potentiated TRPV1 activity via the ET-A receptors (Plant, T. D., C. Zollner, et al. (2006) "Endothelin-1 potentiates capsaicin-induced TRPV1 currents via the endothelin A receptor." Exp Biol Med (Maywood) **231**(6): 1161-4.). In a study performed using TRPV1 deficient mice, it was demonstrated that the sensitization of TRPV1 activity through an ET_A – PKC pathway contributes to ET-1 induced hyperalgesia. It was concluded that it would be better to target TRPV1 rather than ET-1 to be more effective in reducing ET-1 induced pain (Kawamata, T., W. Ji, et al. (2008). "Contribution of transient receptor potential vanilloid subfamily 1 to endothelin-1-induced thermal hyperalgesia." Neuroscience **154**(3): 1067-76). It is therefore likely that even though ET-1 can induce pain, endothelin antagonists may not be useful in treating pain.

13. There also is no evidence either from clinical studies or anecdotally suggesting the use of ET receptor antagonists as analgesic agents. Atrasentan has been clinically evaluated in patients with hormone-refractory prostate carcinoma (Carducci, M. A., R. J. Padley, et al. (2003). "Effect of endothelin-A receptor blockade with atrasentan on tumor progression in men with hormone-refractory prostate cancer: a randomized, phase II, placebo-controlled trial." J Clin Oncol **21**(4): 679-89.), but nothing has been reported

regarding its analgesic activity. Bosentan (an ET receptor antagonist) has been studied in stage IV metastatic melanoma (Kefford, R., J. M. Beith, et al. (2007) "A phase II study of bosentan, a dual endothelin receptor antagonist, as monotherapy in patients with stage IV metastatic melanoma." Invest New Drugs **25**(3): 247-52), but there are no clinical or anecdotal reports of the effect of bosentan therapy on pain. In a randomized, prospective, placebo-controlled, double-blind study of 122 systemic sclerosis patients suffering from digital ulcers, bosentan failed to show a difference in visual analogue pain scores or use of analgesic compared to placebo-treated patients (Korn, J. H., M. Mayes, et al. (2004). "Digital ulcers in systemic sclerosis: prevention by treatment with bosentan, an oral endothelin receptor antagonist." Arthritis Rheum **50**(12): 3985-93). Further, three ET antagonists have been marketed for several years, yet none of them have been reported, clinically or anecdotally, to have any analgesic activity.

14. The '285 patent states that endothelin antagonists treat pain, and the patent lists numerous endothelin antagonists purportedly useful in the treatment of pain. The '285 patent also states that an endothelin antagonist can be used in combination with other compounds useful in the treatment of pain. However, the reference is silent with respect to reversing or reducing opiate tolerance, and as a person skilled in the art I would not make the jump in reasoning required to conclude that coadministration of an opiate analgesic and an endothelin antagonist could reduce opiate tolerance, at least in part because opiate analgesia and opiate tolerance are mediated by different mechanisms.

15. Importantly, the '285 patent states that an endothelin antagonist can treat pain, but the patent completely lacks any proof or data showing that an endothelin antagonist actually is able to treat pain. As a scientist, I view the '285 patent as a document that lists numerous endothelin antagonists and numerous analgesics, and that states in a conclusory fashion that an endothelin antagonist and optional analgesic can be used to treat pain.

16. Contrary to the conclusory statements in the '285 patent, and in addition to the research of others in paragraphs 8-13, my research has shown that an endothelin antagonist, and in particular an ET_A antagonist, does *not* treat pain. This research is exemplified in the specification of the above-identified patent application. In particular, the tail flick method for measuring the effect of an analgesic on rats is disclosed at page 25, line

21 through page 26, line 6 of the specification. This is a standard and well-known method used by persons skilled in the art.

17. The results of the tail flick method are disclosed at pages 28-31 of the specification. In particular, at page 28, lines 17-29 the specification states:

> "**Effect on analgesia**: The control group of rats exhibited tail flick latencies of about 2 seconds. BQ123 treatment did not produce any significant effect on tail flick latency. Morphine (8 mg/kg, s.c.) produced significant analgesia in rats, and the tail flick latencies reached more than 10 seconds (Figure 2). A significant increase in tail flick latencies was observed until three hours after the administration of morphine. The analgesic effect of morphine was significantly potentiated by BQ123. The analgesic effect of morphine not only was significantly greater in BQ123 pretreated rats, but lasted for more than six hours."

It can be seen that the control group (vehicle only) had tail flick latencies of about 2 seconds, and that treatment with an endothelin antagonist (BQ123) *did not produce any* significant effect on tail flick latency. This test shows that an ET_A antagonist has no pain treatment effect, and should be compared to the dramatic effect of morphine, a known analgesic, an tail flick latency. This effect is further demonstrated in Figs. 2-5 and 8 of the specification wherein tail flick latencies for a control group (Veh+Veh, i.e., vehicle only) is essentially *identical* to a group treated with BQ123 (BQ+Veh, i.e., BQ123 and vehicles). Figure 8 shows the same effect for BMS 182,874 as BQ123 in Figures 2-5.

18. My research shows that endothelin antagonists do not alleviate pain. Therefore, based on my training and experience, persons skilled in the art of studying pain, after reading the '285 patent, would use the tail flick method to determine the efficacy of an endothelin antagonist in pain treatment, and would come to the same conclusion as me, i.e., endothelin antagonists *per se* do not treat pain.

19. Also based on my training and experience, a person skilled in the art, after testing an endothelin antagonist for an ability to treat pain and finding that the antagonist was not efficacious, would have no reason to administer the endothelin antagonist with a known analgesic in order to treat pain, let alone reduce or reverse opiate tolerance. In view of the inability of an endothelin antagonist to treat pain, and because of the different opiate

analgesia and opiate tolerance mechanisms, plus the unpredictability in this art, the '285 patent provides no suggestion such that a person skilled in the art would make a jump in reasoning to conclude that an endothelin antagonist could reduce or reverse opiate tolerance.

20. With respect to the '832 patent, the specification states that ET inhibitors "can be reanalyzed for their ability to alleviate pain" (column 6, lines 15-19), and that the method can be "used to alleviate pain in a patient with a condition associated with increased ET-1 levels," such as prostate cancer. However, my research and the research of others has shown that this is not the case. In fact, an ET_A antagonist was used in a clinical study on prostate cancer patients, and no effects on pain were reported. See paragraph 12, above.

21. Like the '285 patent, the '832 patent discloses the treatment of pain using an ET_A antagonist. However, neither reference remotely suggests a reduction or reversal of opiate tolerance. In view of the different mechanisms of opiate analgesics and opiate tolerance, even if an ET_A antagonist could treat pain, a person skilled in the art would not make the jump in reasoning that an ET_A antagonist would be useful to reverse or reduce opiate tolerance.

22. In addition, neither the '285 patent nor the '832 patent actually coadministers an ET_A antagonist and an opiate analgesic, so the effect of such a coadministration is unknown and cannot be predicted. The '285 patent merely discloses that a narcotic can be administered with an ET_A antagonist. No experiments are provided. The '832 patent includes *separate* tests showing that ET-1 can induce pain (column 9, lines 6-25), that morphine can reduce the pain (column 9, lines 26-43), and that ET_A antagonists mediate ET-1 induced pain (column 9, lines 52-63). The '832 patent is silent with respect to the coadministration of an ET_A antagonist and morphine, so no conclusions can be made with respect to the effects of such a coadministration on treating pain, let alone reducing or reversing opiate tolerance which is mediated by a different mechanism.

23. Finally, the '832 patent is directed to pain induced by increased ET-1 levels. However, pain can be mediated by other mechanisms, and the '832 patent teaches that such pain cannot be treated by an ET_A antagonist. Because the mechanism of opiate tolerance is different from opiate analgesic, the present invention operates to reduce opiate

tolerance regardless of whether the pain is related to an increased ET-1 level or other mechanism of pain inducement.

24. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; further, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001, Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or document or any patent resulting therefrom.

Dated: 09/09/2008

Anil Gulati

Anil Gulati M.D., Ph.D.